The end of antibiotic treatment in adults with acute sinusitis-like complaints in general practice? A placebo-controlled double-blind randomized doxycycline trial

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SUMMARY

Background. *Acute sinusitis-like complaints are very common and are usually treated with antibiotics in spite of the lack of evidence for the effectiveness of antibiotic therapy and the increasing number of resistant strains.*

Aim. *To assess the effectiveness of doxycycline in adults with acute sinusitis-like complaints in general practice.*

Method. *The effects of doxycycline in a placebo-controlled, double-blind, randomized trial were assessed in adults consulting their general practitioner (GP) with complaints after a common cold or influenza, pain in the head when bending forward, purulent nasal discharge, predominantly unilateral maxillary pain, toothache, or pain when chewing. Primary outcome events were the resolution of facial pain and the resumption of daily activities. Treatment differences were assessed by means of Kaplan–Meier curves and hazard ratios. The follow-up period was 42 days.*

Results. *No significant difference was found in time to recover between the doxycycline-treated group and the placebo-treated group. However, the adjusted hazard ratio for the group receiving doxycycline was 1.17 (95% CI = 0.87–1.57) for the resolution of pain and 1.31 (95% CI = 0.96–1.78) for the resumption of daily activities. After 10 days, 85% of all patients reported improvement and 60% were completely cured. Side effects were reported by 17% of the doxycycline-treated group, with two patients withdrawing because of side effects.*

Conclusions. *Data from this study indicate that doxycycline does not add to the effectiveness of decongestive nose drops and steam inhalation in treating acute sinusitis-like complaints in general practice adults.*

Keywords: antibiotics; sinusitis; randomized controlled trials.

Introduction

THE incidence of acute sinusitis varies from 15 to 43 episodes per thousand patients per year, indicating diagnostic problems.[1,2] In general practice, sinus culture is neither indicated nor ethical.[3,4] As a routine examination, computerized tomography, as applied by Lindbaek *et al*,[5] is not available in general practice. Compared with antral aspiration, a positive test result in clinical examination has the same diagnostic properties as a positive test result in radiography or ultrasound.[6,7] As there is a lack of agreement between diagnostic studies on the one hand and no 'gold standard' for general practice populations on the other hand, it is nearly impossible to differentiate between a viral common cold and acute sinusitis of bacterial cause.[7-12] The guidelines of the Dutch College of General Practitioners therefore define sinusitis as a complex of sinonasal symptoms.[13]

In The Netherlands, almost all patients with upper respiratory tract infections are treated by their GP.[14] The referral rate is only 5%. International experts advise treating patients with sinusitis with antibiotics.[15,16] Recently, antibiotic treatment has even been discussed for patients with common cold.[17,18] Dutch GPs prescribe doxycycline in 70% of episodes of acute sinusitis-like complaints in adults and ampicillin in a minority of cases.[19] Doxycycline is more effective than ampicillin.[20] Penetration of doxycycline into the sinus secretions is good.[21] Doxycycline targets the predominant pathogens encountered in clinical practice: *Streptococcus pneumoniae* and *Haemophilus influenzae*. The pathogens of cases diagnosed in general practice are not known. Infections with beta-lactamase-producing strains are unusual in The Netherlands, especially in previously untreated adults.[4,22]

Advice for the treatment of acute sinusitis-like complaints should preferably be based on the evidence of placebo-controlled, double-blind, randomized trials. An increasing number of resistant strains, and the misuse of antibiotic agents, emphasizes this necessity.[23-25] Until 1996, there were no convincing studies in which the effectiveness of antibiotics was determined.[26] The aim of this study was to assess the effectiveness of doxycycline in adults with acute sinusitis-like complaints in general practice in a placebo-controlled, double-blind, randomized trial.

Methods

Eligible patients

Between 1 September 1993 and 31 August 1995, patients aged 15–65 years who had consulted their GP at one of the 12 collaborating practices, with 39 000 enlisted patients in total, were eligible if they had experienced symptoms of upper respiratory tract infections for at least five days. The inclusion criteria were based on the diagnostic criteria of the guidelines of the Dutch College of General Practitioners: three main symptoms (complaints after a common cold or influenza; purulent nasal discharge; pain in the maxillary sinuses on bending forward) or two main symptoms and one other symptom (predominantly unilateral maxillary pain, toothache, or pain when chewing. Exclusion criteria were xylomethazoline nose drop treatment lasting more than seven days (because of rebound effects), co-morbidity (diabetes mellitus, heart failure, immune deficiency), pregnancy or breastfeeding, complaints lasting longer than three months, antibiotic treat-

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ment in the previous four weeks, allergy to doxycycline, severe illness resulting from a sinusitis in one of the other sinuses, antacid or iron treatment, referral to an ear, nose and throat specialist, and inability to speak Dutch. The study protocol was approved by the ethics committee of the University of Utrecht. All patients were informed about the background and procedures of the trial, both orally and in writing, and had to give their informed consent. The GPs were trained on how to perform a complete ear, nose, and throat examination.

Baseline characteristics

The patients' medical history was recorded by the GP, applying a computerized questionnaire connected to the medical record.[27] The questionnaire addressed sex, age, health insurance (sick fund, i.e. capitation fee), and date (season), and contained a number of detailed multiple-choice questions about the duration of complaints, the reason for encounter, demand for help, medical history, and ear, nose, and throat examination.

Treatment

Patients were assigned to doxycycline or placebo treatment in blocks of four according to a computer-generated randomization schedule. The trial medication was given for 10 days: two tablets on day 1 and one tablet a day for the nine following days. Doxycycline was supplied as 100 mg coated tablets. Doxycycline and placebo appeared and tasted the same. Xylomethazoline 0.1% nose drops and steam inhalation for 15 minutes were prescribed in both groups three times a day for as long as the patients had complaints. The patients recorded the intake of the study drug in a diary, and the GP counted the remaining tablets at day 10. The patients were advised to take 500 mg of paracetamol as an analgesic agent, if necessary. Blinding of patients and the treatment team was maintained throughout the study.

Adverse effects were recorded by the patients in a diary; these included nausea, vomiting, abdominal pain, diarrhoea, rash, and dizziness.

Follow-up

The patients recorded the degree of facial pain and limitation of daily activities for 10 days using the McGill–Melzack Pain Questionnaire.[28] Absenteeism from school or work, frequency of steaming, and intake of nose drops and analgesics were recorded in a diary. After 10 and 42 days, all patients were seen by the GP for evaluation of their complaints and for a repeat ear, nose, and throat examination.

Outcome events

Primary outcome events were resolution of facial pain (none or mild) and resumption of daily activities (normal level); secondary outcome events were resumption of school or work, intake of analgesics stopped, intake of nose drops stopped, and resolution of all initial complaints except a preceding common cold or influenza 10 and 42 days after inclusion in the trial (Table 1). Meeting all primary and secondary outcome events was defined as being completely cured.

Data analyses

The principal aim of the analysis was to compare the duration of facial pain and restricted daily activities in each treatment group. To assess a minimal relevant difference of one day (standard deviation of two days), we needed a minimum number of 84 subjects to be included in each treatment group (alpha = 0.05 and beta = 0.10). The analysis was based on the intention-to-treat principle.[29] Survival analysis techniques were used to estimate the duration of complaints (SPSS statistical package). With survival analysis techniques, one can use all the available follow-up information, while patients have different follow-up duration times.[30] Kaplan–Meier curves were used for graphic comparison. Those patients who still had complaints at the end of the study were censored on the last day of observation. To estimate the independent effect of doxycycline, the Cox proportional hazard model was used, and hazard ratios (i.e. the risk of the outcome event per unit of time for patients randomly assigned to doxycycline divided by the risk for those randomly assigned to placebo, with corresponding 95% confidence intervals) were calculated.[31] *P* values were obtained from the Cox model; $P \leq 0.05$ was considered to be significant. The assumption of the proportional hazard was tested, and the hazard ratio was adjusted for baseline incomparability. Interaction between the effect of the treatment and season, all possible combinations of inclusion criteria, duration of complaints before randomization, relapse of sinusitis-like complaints, cough, maxillofacial pressure pain, nasal speech, and cervical lymphatic glands were assessed using the Cox model.[7-9,32] The precision of the estimates was described by means of 95% confidence intervals.

Results

Patient characteristics

From 697 patients with upper respiratory tract infections, 192 were randomized (Figure 1). The excluded group (Table 2) differed from the randomized by having more women (79%), more patients whose complaints had lasted for longer than 14 days (32%), and more patients whose reason for requesting help was 'complaints lasting too long' (57%). Compared with the randomized sample, patients who refused were more likely to have no sick fund insurance, 'sinusitis complaints' as a reason for

Table 1. Median day of cure, according to assigned treatment, with crude and adjusted hazard ratios.

Variable	No. of patients on day 1		Median day of cure (95% CI)		*P* value	Adjusted[a] hazard ratio (95% CI)
	Doxycycline	Placebo	Doxycycline	Placebo		
Resolution of pain	85	91	4 (3.2–4.8)	5 (4.2–5.8)	0.25	1.17 (0.87–1.57)
Resumption of daily activities	84	85	5 (4.3–5.8)	6 (4.9–7.1)	0.12	1.31 (0.96–1.78)
Resumption of school/work	48	32	6 (4.9–7.1)	4 (2.6–5.4)	0.09	0.70 (0.44–1.11)
Intake of analgesics stopped	56	60	5 (3.8–6.2)	7 (5.8–8.2)	0.43	1.17 (0.81–1.68)
Intake of nose drops stopped	92	92	7(6.0–8.0)	8 (7.5–8.5)	0.23	1.19 (0.89–1.59)

[a]Adjusted for reason for encounter, demand for help, season, relapse of sinusitis, nasal speech, and cervical lymphatic glands.

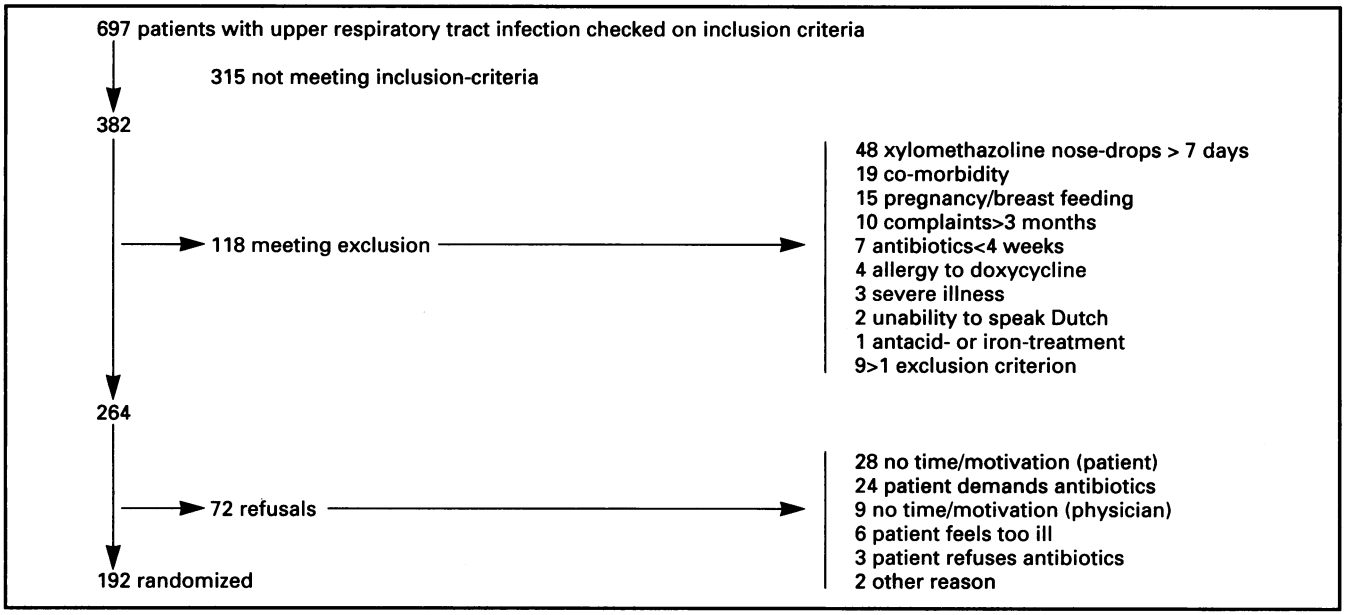

Figure 1. Number of patients checked on inclusion and exclusion criteria and refusals.

Table 2. Baseline characteristics of excluded patients and refusals.

Variable	Excluded	Refusals
No. of patients	118	72
Women (%)	79	65
Mean age in years (SD)	36.3 (11.3)	33.7 (10.3)
Sick fund (%)	62	58
Season (%)		
Spring/summer	24	21
Autumn/winter	76	79
Inclusion criteria (%)		
Beginning with common cold	93	90
Purulent nasal discharge	80	85
Pain at bending	91	94
Predominantly unilat. maxillary pain	77	90
Toothache/pain chewing	53	44
Duration of complaints before randomization in days (%)		
5–9	39	54
10–14	29	22
> 14	32	24
Reason for encounter (%)		
Headache	34	26
Sinusitis complaints	27	46
Cold/cough	22	25
Other complaints	17	3
Reason for requesting help (%)		
Too much hindrance	28	33
Complaints lasting too long	57	35
Treatment expected	12	28
Other	3	4

encounter, 'treatment expected' as a reason for requesting help, and a predominantly unilateral maxillary pain.

Table 3 shows the baseline characteristics of all randomized patients, and the slight differences between treatment groups with regard to reason for encounter, demand for help, season, relapse of sinusitis, nasal speech, and cervical lymphatic glands. The majority of the randomized patients were female, insured by sick fund, randomized in autumn or winter, and randomized within two weeks of the onset of complaints. Twenty-seven per cent of the randomized patients met all five inclusion criteria; 41% met four inclusion criteria (not in Table 3).

Outcome during the 10 days of treatment

More than 50% of the patients were free of pain at day 4 in the doxycycline-treated group and at day 5 in the placebo-treated group and resumed normal daily activities at days 5 and 6 respectively (Table 1). The percentage of patients continuing to have pain after randomization tended to decrease more rapidly in doxycycline recipients than in placebo recipients and was most pronounced after three to four days of therapy (Figure 2). The same trend was found in the resumption of daily activities and in the secondary outcome events (stopping of analgesic intake and stopping of nose drop intake). Although the corresponding hazard ratios indicate a marginally better response to the antibiotic, differences were not significant. Resumption of school or work tended to occur later in patients receiving doxycycline. Control for baseline incomparability did not result in a difference between the crude and adjusted hazard ratios (not in Table 1). There was no interaction between the treatment and the planned subgroups.

The patients' compliance regarding steaming and the mean intake of analgesics was the same in both treatment groups, and the latter did not exceed one tablet a day (not in Table 1). The remaining trial tablets as recorded by the patients did correspond to the numbers counted by the GP at day 10. Trial medication was discontinued in 12 patients in the doxycycline-treated group and eight in the placebo-treated group. The reason was either that antibiotics were given because of treatment failure (three and seven patients respectively) or recurrence (five and one respectively), or that side effects were experienced (four and none respectively). But, according to the intention-to-treat principle, they were included in the analysis. No complications of sinusitis were reported. Lost to follow-up were 11 patients, six at day 10 (four in the doxycycline-treated group, two of them because of vomiting and abdominal pain) and five at day 42 (three in the doxycycline-treated group). Patients who discontinued trial medication did not differ from the other randomized patients in demographic or clinical parameters at the beginning of the study.

Table 3. Baseline characteristics of study patients according to assigned treatment.

Variable	Placebo	Doxycycline
No. of patients	94	98
Women (%)	66	63
Mean age in years (SD)	36.8 (11.8)	36.9 (11.3)
Sick fund (%)	67	66
Season (%)		
Spring/summer	23	36
Autumn/winter	77	64
Inclusion criteria (%)		
Beginning with common cold	93	92
Purulent nasal discharge	80	86
Pain at bending	89	90
Predominantly unilat. maxillary pain	79	80
Toothache/pain chewing	53	47
Duration of complaints before randomization in days (%)		
5–9	56	54
10–14	25	25
>14	19	21
Reason for encounter (%)		
Headache	40	44
Sinusitis complaints	30	19
Cold/cough	26	23
Other complaints	4	14
Reason for requesting help (%)		
Too much hindrance	27	38
Complaints lasting too long	46	47
Treatment expected	23	14
Other	4	1
History (%)		
Blockage of nose/anosmia/cacosmas	89	94
Facial pain	96	92
Relapse of sinusitis-like complaints	37	44
Sinonasal operations	14	14
Malaise increasing during the day	69	64
Pain in ear or throat	34	33
Cough	65	66
Smoking	40	43
Allergy/asthma/COPD	20	22
Ear, nose and throat examination (%)		
Maxillofacial pressure pain	81	85
Nasal speech	27	20
Septum deviation	16	10
Discharge on inferior concha	9	14
Post-nasal drip	9	8
Otitis media	14	13
Cervical lymphatic glands	37	45
Nasal polyp, septum spine, caries, tonsillitis and use of anti-allergic nasal spray	< 4	< 4

Seventeen patients receiving doxycycline reported side effects: nausea (nine), vomiting (five), abdominal pain (five), diarrhoea (two), rash (two), and dizziness (one). In the placebo-treated group, two patients reported nausea.

Outcome after 10 and 42 days

No differences were found in the secondary outcome events: pain in the head at bending forward and purulent nasal discharge (Table 4). Possibly, maxillary pain tends to disappear more slowly in the doxycycline-treated group, as does toothache/pain when chewing in the placebo-treated group.

After 10 days, 60% of all patients were completely cured, according to our criteria. A total of 85% of all patients reported an improvement after 10 days. After 42 days, 90% of all patients were completely cured, with no differences between treatment groups.

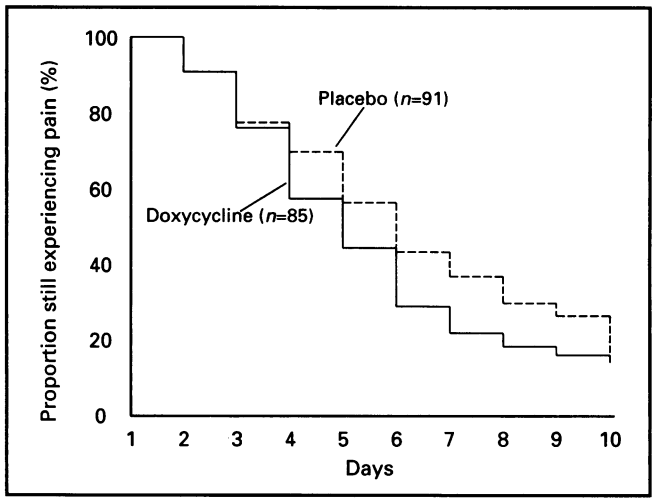

Figure 2. Kaplan–Meier curves for sinusitis-related pain, according to assigned treatment.

Discussion

Data from this study indicate that there is insufficient evidence for the effectiveness of doxycycline in adults with acute sinusitis-like complaints in general practice who were treated with decongestive nose drops and steam inhalation. Side effects were reported by 17% of the doxycycline-treated group. We did not succeed in identifying subgroups that do benefit from the antibiotic. After 10 days, 85% of the patients in both treatment groups reported an improvement and 60% were completely cured. After six weeks, 10% of the patients still had one or more complaints in both groups. Possibly, there is a trend to a more rapid cure (in one day) using doxycycline. However, in view of the reported side effects and the problem of increasing bacterial resistance, the observed hazard ratios for facial pain and restricted daily activities are not clinically useful.

Regarding the internal validity of our study, control for baseline incomparability did not influence the results.[33] The total withdrawal rate was 10%. Eleven patients could only be partially analysed because they were lost to follow-up. Whether this loss was related to the treatment is unknown, but the figures are too small to influence the results. Compliance seems to be good, because remaining trial tablets as recorded by the patients corresponded to the numbers counted by the GP. The external validity of our study was enlarged by the use of the computer-based medical record, in which a warning system was implemented to draw attention to eligible patients.[34] With regard to age, sex, season of onset, demand for help, reason for encounter, and inclusion complaints, the study population corresponds to findings in other studies.[2,7] Baseline differences between the excluded and the randomized patients were caused particularly by pregnancy, breastfeeding, and chronic complaints. In the refusal population, there was a higher frequency of patients without sick fund insurance. Their more frequent demand for antibiotic treatment could be caused by the severity of their complaints or by the fact that they have to pay for every single consultation. Only a bacterial sinusitis should be treated with antibiotics, but antral aspiration to assess a bacterial cause is not available in general practice. Outcomes of sinus culture in a clinical setting are not applicable in general practice because of selection.[35] The advantage of our study, conducted in an almost unselected population, is that it

Table 4. Numbers (%) of patients with symptoms at day 1, 10, and 42, with adjusted *P* values, according to treatment.

Treatment	Day 1[a]	Day 10	Day 42	*P* value
Pain at bending				
Doxycycline	88	14 (16)	1 (1)	
Placebo	84	16 (19)	2 (2)	
Total	172	30 (17)	3 (2)	0.53
Purulent nasal discharge				
Doxycycline	84	18 (21)	5 (6)	
Placebo	75	19 (25)	5 (7)	
Total	159	37 (23)	10 (6)	0.86
Predominantly unilateral maxillary pain				
Doxycycline	78	18 (23)	4 (5)	
Placebo	74	9 (12)	1 (1)	
Total	152	27 (18)	5 (3)	0.07
Toothache/pain checking				
Doxycycline	46	1 (2)	0 (4)	
Placebo	50	8 (16)	2 (6)	
Total	96	9 (9)	2 (5)	0.07

[a]All numbers at day 1 = 100%.

corresponds with generally accepted procedures in general practice.

This study agrees with the results of Rantanen's trial[36] on doxycycline and van Buchem's recent study[37] on amoxycillin in outpatients selected by means of radiography. Ekdahl's results[38] were smiliar to ours: an improvement in 83% of both treatment groups after 10 days, with 13% of the treatment group experiencing side effects. Using computerized tomography as a reference standard, Lindbaek[5] found penicillin V and amoxycillin to be significantly more effective than placebo in a highly selected population. Differences between our results and those of Lindbaek[5] might be caused by our supporting treatment with decongestive nose drops and steam inhalation. The decongestive effect of nose drops on nasal mucosa reduces obstruction of the ostium and the pain caused by it, and supports aeration of the sinus.[39] Nose-drops also influence the level of nasal nitric oxide in the sinuses, which has been suggested as playing an important role in mucociliary activity.[40] Steam inhalation seems to have a positive short-term effect on acute sinusitis-like complaints.[41] Therefore, the small differences between doxycycline and placebo in our study might be a result of the supporting therapy. The possible viral or osteomatal dysfunctional origin of sinusitis-like complaints could be another reason for the lack of effectiveness of antibiotics.[42,43] Bacterial infection with resistant strains could be a further explanation for the ineffectiveness found. But, in The Netherlands and the United Kingdom, resistant strains are less frequent, especially in previously untreated patients.[4,14,22]

We conclude that acute sinusitis-like complaints in general practice are usually self-limiting, and that doxycycline does not add a clinically useful effect to treatment with decongestive nose drops and steam inhalation in an unselected population. Although an individual patient might benefit from antibiotic treatment, we could not identify subgroups that would do so. Therefore, we recommend that antibiotics should not be given in the first instance. An increasing number of resistant strains and the misuse of antibiotic agents might provide support for this advice.

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A message from the President: Dame Josephine Barnes DBE DM FRCP FRCS FRCOG

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The existence of the Christmas appeal makes it possible for the Fund to send extra finance to those whom we help. The many letters and cards received in the office are testimony to the appreciation of our beneficiaries and especially their children.

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Contributions marked "CHRISTMAS APPEAL" may be sent to the Secretary, Royal Medical Benevolent Fund, 24 King's Road, Wimbledon, London SW19 8QN or to the Treasurer or Medical Representative of your local guild of the RMBF.

Dame Josephine Barnes, President